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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,469	07/19/2001	Markus Schweitzer	264/217	1747

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EXAMINER
FORMAN, BETTY J

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/910,469	SCHWEITZER ET AL.	
	Examiner	Art Unit	
	BJ Forman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-326* is/are pending in the application.

4a) Of the above claim(s) *1-274* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *275-326* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4/02 10/03*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group 81, Claims 275-326 in papers filed 10 April 2003 is acknowledged.

Inventorship

2. In view of the papers filed 10 April 2003, the inventorship in this nonprovisional application has been changed by the deletion of Richard R. Anderson, Michael Fiechtner and Jill Orwick.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Specification

3. The disclosure is objected to because of the following informalities:

Page 36, line 29 and page 37, line 1 contain two commas separated by a space ", ," which suggests that a word is missing between the commas.

The specification recites "CNA" throughout the text of the specification. However, the specification fails to define or describe the meaning of the term. Because the meaning of the term is not understood in the context of the specification and because the specification does not define or describe the term, the specification is objected to for using an undefined term.

Appropriate correction is required.

Information Disclosure Statement

4. The references listed on the 1449 received 18 October 2001 have been reviewed and considered as noted on the 1449. Only the English-language abstracts of the non-English language references have been reviewed as noted on the 1449.

The non-U.S. Patent references listed on the 1449 received 16 April 2002 have not been reviewed because copies of the references have not been supplied.

Copies of the initialed 1449s are enclosed with this action.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 275-326 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 275-326 are indefinite in Claim 275 because the claim is drawn to a method for modifying a nucleic acid selected from 1) a target nucleic acid and 2) the nucleic acid of a conjugate comprising a NA and SBU. However, the method steps include "contacting the conjugate" and "incubating the mixture". Therefore, it is unclear whether the method steps modify a target nucleic acid as claimed.

b. Claims 275-326 are indefinite in Claim 275, line 2, for "the nucleic acid"; step a) for "the action of the enzyme"; step b), line 1, for "the mixture"; and step b), lines 1-2 for "the functioning" because all of the recitations lack proper antecedent basis. It is suggested that claim 275 be amended to provide proper antecedent basis.

c. Claim 293 is indefinite for the recitation "contacting the conjugate with an RNAase H activity" because it is unclear whether the RNAase H enzyme is in the mixture or merely the activity of the enzyme.

d. Claims 301-308 are each indefinite for the recitation "the point of activity" because the recitation lacks proper antecedent basis in Claim 275.

e. Claims 301-308 are each indefinite for the recitation "the point of conjugation" because the recitation lacks proper antecedent basis in Claim 275.

f. Claims 325 and 326 contains the trademark/trade name BIODIPY, KODAK, AND Black Hole Quencher. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson,* 218 USPQ 1020 (Bd.

App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe labels and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 275-287, 289-290, 292, 297-314, 319-321 and 323-325 are rejected under 35 U.S.C. 102(b) as being anticipated by Kool (U.S. Patent No. 6,077,668 issued 20 June 2000).

The claims are broadly drawn to methods of modifying a nucleic acid comprising the steps of contacting a conjugate comprising a nucleic acid and synthetic binding unit (e.g. nucleic acid analog) with an enzyme with reagents and under conditions for nucleic acid modification. The claimed conjugate is encompasses a circular template comprising analogs, a primer comprising analogs, and a multimer comprising analogs all of which are taught by

Kool as discussed below. Because all of these conjugates are encompassed by the claims, various methods of modifying the conjugates are also encompassed by the claims.

Regarding Claim 275, Kool discloses a method for enzymatically modifying a nucleic acid, the method comprising: contacting conjugate comprising a nucleic acid and synthetic binding unit (i.e. circular template containing nucleic acid analog, Column 9, lines 26-33 and Column 13, line 56-Column 14, line 11) with an enzyme with utilizes naturally occurring nucleic acids as a substrate and other reagents for enzyme action and incubating the mixture under conditions suitable for enzyme functioning for a period of time sufficient to effect modification of the nucleic acid (Column 5, lines 34-53).

Regarding Claim 276, Kool discloses method wherein the reagents include a nucleic acid with hybridizes to the nucleic acid of the conjugate i.e. primer (Column 5, lines 34-53).

Regarding Claim 277, Kool discloses the method wherein the other reagents includes modified (i.e. labeled) nucleoside triphosphates (Column 5, lines 34-53).

Regarding Claim 278, Kool discloses the method wherein the enzyme is selected from a polymerase (Column 5, lines 14-26), a ligase (Column 10, lines 9-64) and a restriction endonuclease (Example 3, Column 26, Scheme II).

Regarding Claim 279, Kool discloses the method wherein the enzyme is ligase and the conjugate is modified by ligation of a terminus of the nucleic acid to at least one additional nucleic acid e.g. linker (Column 10, line 27-Column 11, line 2).

Regarding Claim 280, Kool disclose the method wherein the ligation is template dependent and the nucleic acid of the conjugate and the additional nucleic acids are hybridized to adjacent sequences of a template i.e. splint (Example 26, Column 45).

Regarding Claim 281, Kool discloses the method wherein the ligation is template independent and the nucleic acid of the conjugate and the additional nucleic acids are single stranded (Column 10, line 27-Column 11, line 2).

Regarding Claim 282, Kool discloses the method wherein the ligase is T4 RNA ligase (Column 10, lines 62-65).

Regarding Claim 283, Kool discloses the method wherein the ligation is blunt-ended and the nucleic acid of the conjugate and the additional nucleic acids (i.e. adapter) are double stranded i.e. adapter is hybridized to the precircle thereby juxtaposing the 5' and 3' ends of the precircle which are then ligated (Column 10, lines 59-64 and Column 11, lines 3-24).

Regarding Claim 284, Kool discloses the method wherein the enzyme is a polymerase, wherein the nucleic acid of the conjugate has an unblocked 3' terminus, wherein the other reagents comprise a template to which the unblocked terminus hybridizes and wherein the nucleic acid is modified by the addition of at least one nucleoside complementary to the template at the 3' terminus i.e. in this embodiment, Kool teaches a biotinylated (analog) oligonucleotide as the conjugate having an unblocked 3' terminus which, when contacted with the circular template and a polymerase, is modified by addition of a nucleoside complementary to the template (Example 31, Column 51, line 61-Column 52, line 17).

Regarding Claim 285, Kool discloses the method of Claim 284 wherein the resulting modified conjugates are sequenced using dideoxynucleotides (Example 17, Column 39, lines 15-44).

Regarding Claim 286, Kool discloses the method of Claim 284 wherein a labeled nucleotide is added to the conjugate (Example 31, Column 52, lines 3-7).

Regarding Claim 287, Kool discloses the method of Claim 284 wherein the template is derived from a biological sample i.e. the circular template is derived from any organism (Column 10, lines 20-24).

Regarding Claim 289, Kool discloses the method of Claim 284 wherein the polymerase is selected from DNA polymerase, RNA polymerase and reverse transcriptase (Column 5, lines 14-33).

Regarding Claim 290, Kool discloses the method of Claim 284 wherein at least a portion of the template is amplified i.e. a multimer is produce comprising multiple copies of the circular template (Example 31, Column 51, line 61-Column 52, line 17).

Regarding Claim 292, Kool discloses the method of Claim 284 further comprising contacting the conjugate with a restriction endonuclease and wherein the conjugate comprises a recognition sequence 5' of the 3' terminus which hybridizes to the template and wherein at least a portion of the template is amplified by strand displacement (Column 8, lines 36-57 and Column 9, lines 56-Column 10, line 9 and Fig. 1).

Regarding Claim 297, Kool discloses the method of Claim 275 wherein the enzyme is a restriction endonuclease and the other reagents comprise a target nucleic acid (i.e. short DNA strand) which hybridizes to the conjugate and wherein the conjugate and the target are cleaved by the restriction endonuclease (Column 21, lines 1-10).

Regarding Claim 298, Kool discloses the method of Claim 275 wherein the enzyme is a restriction enzyme wherein the other reagents comprise a target nucleic acid to which the conjugate hybridizes and wherein the conjugate (i.e. multimer) is cleaved by the restriction enzyme but not the target (i.e. circular template) (Example 31, Column 51, line 61-Column 52, line 17 and Fig. 1).

Regarding Claim 299, Kool discloses the method of Claim 275 wherein the enzyme is a restriction enzyme wherein the other reagents comprise a target nucleic acid to which the conjugate hybridizes and wherein the target (i.e. circular template) is cleaved by the restriction enzyme but conjugate (i.e. multimer) not the (Example 31, Column 51, line 61-Column 52, line 17 and Fig. 1). In this embodiment, the conjugate is the circular template comprising analogs and the target is the multimer product which is cleaved by the restriction enzyme. As stated above, the claims are broadly drawn to encompass numerous and various embodiments as disclosed by Kool.

Regarding Claim 300, Kool disclose the method of Claim 275 wherein the enzyme is RNAase H wherein other reagents comprise an RNA target to which a portion of the conjugate hybridizes and wherein the conjugate is degraded (i.e. cleaved) by the RNAase H (Column 22, lines 39-45).

Regarding Claims 301-308, Kool discloses the method of Claim 275 wherein the point of activity of the enzyme is at the point of conjugation of the nucleic acid and the synthetic binding unit i.e. the analog-containing primer is contacted by the polymerase and therefore the point of activity for the primer (Column 8, lines 37-57; Column 11, line 51-Column 12, line 40; and Column 18, lines 48-62).

Regarding Claims 309-314, Kool discloses the method wherein the SBU is an oligomer comprising of a backbone connecting monomeric units (i.e. nucleotides) and a recognition moiety (i.e. base) which provides specific interaction with a synthetic addressing unit wherein the moiety is a six membered ring comprising carbon i.e. a pyranosyl ring and wherein the molecular interaction is via hydrogen bonding i.e. hybridization and wherein the moiety comprises a nitrogen heterocycle i.e. base (e.g. pRNA, Column 13, line 57-Column 14, line 11).

Regarding Claim 319, Kool discloses the method wherein the nucleic acid is selected from the group consisting of DNA, RNA and chemically modified nucleic acids (Column 8, lines 61-66).

Regarding Claim 320, Kool discloses the method wherein the nucleic acid is selected from the group consisting of phosphorothioate nucleic acids, phosphorodithioate nucleic acids, methylphosphonate nucleic acids, 2'-o-methyl RNA, and 2'-fluoro RNA (Column 13, line 57-Column 14, line 11).

Regarding Claim 321, Kool discloses the method wherein the nucleic acid is PNA (Column 13, lines 57-65).

Regarding Claim 323, Kool discloses the method wherein the conjugate further comprises at least one labeling moiety e.g. the primer as conjugate is labeled (Column 13, lines 26-36).

Regarding Claim 324, Kool discloses the method wherein label is selected from fluorescent moiety, visible dye moiety, raditoactive moiety, chemiluminescent moiety, biotin moiety (Column 17, lines 36-59).

Regarding Claim 325, Kool discloses the method wherein the labeling moiety is a fluorescent dye selected from fluorescein dyes, rhodamine dyes, Texas red dyes, Oregon green (Column 17, lines 50-59).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 288 and 291 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kool (U.S. Patent No. 6,077,668 issued 20 June 2000) in view of Zhang et al (U.S. Patent No. 5,876,924, issued 2 March 1999).

Regarding Claim 288, Kool discloses a method for enzymatically modifying a nucleic acid, the method comprising: contacting a conjugate comprising a nucleic acid and synthetic

binding unit (i.e. circular template containing nucleic acid analog, Column 9, lines 26-33 and Column 13, line 56-Column 14, line 11) with an enzyme with utilizes naturally occurring nucleic acids as a substrate and other reagents for enzyme action and incubating the mixture under conditions suitable for enzyme functioning for a period of time sufficient to effect modification of the nucleic acid (Column 5, lines 34-53) wherein the template is derived from a biological sample i.e. the circular template is derived from any organism (Column 10, lines 20-24) but they do not specifically teach the claimed organisms and samples. However, Zhang et al teach a similar method for modifying a nucleic acid comprising: contacting a conjugate comprising a nucleic acid and synthetic binding unit (i.e. bead modified probe, Column 7, lines 8-30) with an enzyme with utilizes naturally occurring nucleic acids as a substrate and other reagents for enzyme action and incubating the mixture under conditions suitable for enzyme functioning for a period of time sufficient to effect modification of the nucleic acid (Column 43, line 56-Column 44, line 40) wherein the sample is selected from the group consisting of human materials and viral cultures whereby clinically important samples are sensitively detected rapidly(Column 3, lines 3-9). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the human and viral sample detection of Zhang et al to the organism detection of Kool based on the clinical importance of human and viral detection as taught by Zhang et al (Column 3, lines 3-9).

Regarding Claim 291, Kool teaches the method wherein the polymerase is a thermostable polymerase (Column 13, lines 22-24) but they do not specifically teach thermocycling conditions. However, Zhang et al teach the similar method wherein the template is amplified utilizing a thermostable polymerase and thermocycling conditions whereby sequence-specific amplification is performed (Column 14, lines 1-67). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the thermocycling conditions of Zhang et al to the amplification of Kool to thereby provide amplification temperatures specific for the sequence to be amplified for the expected

benefit of optimizing conditions for sequence-specific amplification as taught by Zhang et al (Column 14, lines 1-67).

11. Claim 293 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kool (U.S. Patent No. 6,077,668 issued 20 June 2000) in view of Berninger et al (U.S. Patent No. 5,194,370 issued 16 March 1993).

Regarding Claim 293, Kool discloses a method for enzymatically modifying a nucleic acid, the method comprising: contacting a conjugate comprising a nucleic acid and synthetic binding unit (i.e. circular template containing nucleic acid analog, Column 9, lines 26-33 and Column 13, line 56-Column 14, line 11) with an enzyme with utilizes naturally occurring nucleic acids as a substrate and other reagents for enzyme action and incubating the mixture under conditions suitable for enzyme functioning for a period of time sufficient to effect modification of the nucleic acid (Column 5, lines 34-53) wherein the polymerase is RNA polymerase and containing RNAase H activity (Column 22, lines 39-45) but does not teach the polymerase is in a mixture comprising reverse transcriptase. However, mixtures of RNA polymerase, reverse transcriptase and RNAase H were well known in the art at the time the claimed invention was made as taught by Berninger et al (Column 13, lines 55-67). Furthermore they teach the mixture produces nucleic acids functionally identical to the starting nucleic acids (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the polymerase mixture of Berninger et al to the RNA synthesis of Kool for the expected benefit of obtaining RNA molecules functionally identical to the starting RNA molecules as taught by Berninger et al (Abstract).

12. Claim 294-296 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kool (U.S. Patent No. 6,077,668 issued 20 June 2000) in view of Nelson et al (Methods in Enzymology, 1979, 68: 41-50).

Regarding Claims 294-296, Kool discloses a method for enzymatically modifying a nucleic acid, the method comprising: contacting a conjugate comprising a nucleic acid and synthetic binding unit (i.e. circular template containing nucleic acid analog, Column 9, lines 26-33 and Column 13, line 56-Column 14, line 11) with an enzyme with utilizes naturally occurring nucleic acids as a substrate and other reagents for enzyme action and incubating the mixture under conditions suitable for enzyme functioning for a period of time sufficient to effect modification of the nucleic acid (Column 5, lines 34-53) wherein the polymerase is RNA polymerase and containing RNAase H activity and a labeled nucleic acid is added to the conjugate (Column 22, lines 39-45) but they do not teach the enzyme is a terminal transferase wherein a homopolymeric tail is added to the conjugate. However, terminal transferase addition of homopolymeric tails was well known in the art at the time the claimed invention was made as taught by Nelson et al who teach that addition of homopolymeric tails using terminal transferase eliminates the need for restriction sites and results in successful infection (page 42, second full paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the terminal transferase addition of homopolymeric tails as taught by Nelson et al to the nucleic acid addition of Kool. One of ordinary skill in the art would have been motivated to do so based on the advantages taught by Nelson et al i.e. eliminates the need for restriction sites and results in successful infection (page 42, second full paragraph).

13. Claims 322 and 326 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kool (U.S. Patent No. 6,077,668 issued 20 June 2000) in view of Lannigan et al (U.S. Patent No. 6,399,302, filed 20 August 1999).

Regarding Claims 322 and 326, Kool discloses a method for enzymatically modifying a nucleic acid, the method comprising: contacting a conjugate comprising a nucleic acid and synthetic binding unit (i.e. circular template containing nucleic acid analog, Column 9, lines 26-33 and Column 13, line 56-Column 14, line 11) with an enzyme with utilizes naturally occurring nucleic acids as a substrate and other reagents for enzyme action and incubating the mixture under conditions suitable for enzyme functioning for a period of time sufficient to effect modification of the nucleic acid (Column 5, lines 34-53) wherein the polymerase is RNA polymerase and containing RNAase H activity and a labeled nucleic acid is added to the conjugate (Column 22, lines 39-45) but they do not teach the nucleic acid is an aptamer wherein the conjugate is labeled with a quencher moiety. However, quencher labeled aptamers were well known in the art at the time the claimed invention was made as taught by Lannigan et al. who further teach that aptamers have the ability to form an array of shapes, sizes and configurations and therefore are capable of forming specific binding pairs with almost any compound (Column 1, lines 49-63). They further teach that the quencher labeled aptamers permits real-time detection of binding events (Column 10, lines 57-61). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the quencher-labeled nucleic acid aptamers of Lannigan et al to the nucleic acids of Kool to thereby provide nucleic acids which would form binding partner with virtually

any compound wherein the binding event would be detected over time as taught by Lannigan et al (Column 1, lines 49-63 and Column 10, lines 57-61) for the expected benefit of detecting a binding partner for any compound for which a binding partner is desired (Column 1, lines 49-63).

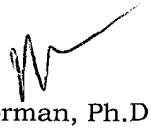
Conclusion

14. Claims 315-318 are free of the prior art of record and may be placed in condition for allowance following resolution of the above rejections.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



BJ Forman, Ph.D.
Primary Examiner
Art Unit: 1634
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